HED DOC. NO. 014311

DATE: 8/28/00

MEMORANDUM

SUBJECT: ***Diaminochlrotriazine (DACT)*** - Report of the Hazard Identification Assessment Review Committee.

FROM: Roger Hawks, Toxicologist.
Reregistration Branch III
Health Effects Division (7509C)

THROUGH: Jess Rowland, Co-Chair
and
Elizabeth Doyle, Co-Chair
Hazard Identification Assessment Review Committee
Health Effects Division (7509C)

TO: Cathy Eiden, Risk Assessor
Reregistration Branch III
Health Effects Division (7509C)

PC Code: None (the compound is the common terminal metabolite of the triazine herbicides atrazine, simazine and propazine) *File under PC code for atrazine - 080803*

On May 4, 2000, the Health Effects Division (HED) Hazard Identification Assessment Review Committee (HIARC) reviewed the recommendations of the toxicology reviewer for diaminocholorotriazine (DACT, G-28273) with regard to the acute and chronic Reference Doses (RfDs) and the toxicological endpoint selection for use as appropriate in occupational/residential exposure risk assessments. HIARC met on this compound in Fall of 1999. The discussion during this meeting led to the conclusion that the prudent course of action would be to reschedule another HIARC meeting to be held following receipt of a pending 28 day luteinizing hormone surge study using atrazine, simazine and DACT. A draft interim report of this study was received (MRID 45058701) in mid-March, 2000, and a HIARC meeting was scheduled shortly thereafter. The potential for increased susceptibility of infants and children from exposure to DACT was also evaluated as required by the Food Quality Protection Act (FQPA) of 1996. The conclusions drawn at this meeting are presented in this report.

Committee Members in Attendance

Members present were:
Elizabeth Mendez, David Nixon, Yung Yang, Beth Doyle, Jonathon Chen, Jess Rowland, Brenda Tarplee, Bill Burnam, Vicki Dellarco, Pam Hurley

Member(s) in absentia: Tina Levine

Data evaluation prepared by: Roger Hawks, Reregistration Branch III

Also in attendance were: Karl Baetcke, HED Richard Hill, OPPTS

Data Evaluation / Report Presentation

Roger Hawks
Toxicologist

1. INTRODUCTION

On May 4, 2000, the Health Effects Division (HED) Hazard Identification Assessment Review Committee (HIARC) reviewed the recommendations of the toxicology reviewer for diaminocholorotriazine (DACT, G-28273) with regard to the acute and chronic Reference Doses (RfDs) and the toxicological endpoint selection for use as appropriate in occupational/residential exposure risk assessments. HIARC met on this compound in Fall of 1999. The discussion during this meeting led to the conclusion that the prudent course of action would be to reschedule another HIARC meeting to be held following receipt of a pending 28 day luteinizing hormone surge study using atrazine simazine and DACT. A draft interim report of this study (MRID 45058701) was received in mid-March of, 2000, and a HIARC meeting was scheduled shortly thereafter. The potential for increased susceptibility of infants and children from exposure to DACT was also evaluated as required by the Food Quality Protection Act (FQPA) of 1996. The conclusions drawn at this meeting are presented in this report.

2. HAZARD IDENTIFICATION

2.1 Acute Reference Dose (RfD) - Subpopulation: Females 13-50

Study Selected: Developmental Toxicity (Rat) Guideline #: 83-3

MRID No.: 41392402

Executive Summary:

In a developmental toxicity study (MRID 41392402) Diaminochlorotriazine (DACT, the terminal mammalian metabolite of both atrazine and simazine), 98.2 % a.i. was administered to 130 Sprague-Dawley females, 26/dose, by gavage at dose levels of 0, 2.5 , 25, 75 or 150 mg/kg/day from days 6 through 16 of gestation. Animals were sacrificed and uteri removed for evaluation on gestation day 20.

Maternal body weight gain for the 20 day gestation period was reduced 33.2% (p# 0.05), compared to controls, at 150 mg/kg/day. Body weight gain during the dosing period was reduced 27.9% (not significant) and 71% (p# 0.05) at the 75 and 150 mg/kg/day groups, respectively, compared to controls. Food consumption for the 20 day gestation was reduced by 21.1% (p# 0.05), compared to controls, at 150 mg/kg/day. Body weight gains and food consumption were not affected at any other dose group compared to control. There were no treatment-related effects in mortality or clinical signs in any dose group.
The maternal LOAEL is 75 mg/kg/day, based on decreased body weight gain during dosing. The maternal NOAEL is 25 mg/kg/day.

Resorptions per dam were increased from 0.8 in controls to 2.6 (p# 0.05) in the 150 mg/kg/day group. Postimplantation loss was increased from 5.6% in controls to 18.9% (p# 0.05)in the 150 mg/kg/day group.

Gravid uterine weight per dam was decreased from 72.3 gm. in the controls to 55.9 gm. (p# 0.05) at 150 mg/kg/day. Mean fetal weights were reduced 19.1% and 18.5% in males and females, respectively, at the 150 mg/kg/day dose group compared to controls (p# 0.05 for both). Mean fetal weights were reduced 9% and 7.9% for males and females, respectively at the 75 mg/kg/day group (p# 0.05 for both). Absent renal papilla were seen in 22% of the 150 mg/kg/day fetuses compared to 3.3% of the control fetuses (p# 0.05). Pitted kidneys were seen in 4.8% of the 150 mg/kg/day fetuses and in 0% of the control fetuses (p# 0.05). When evaluated using either the fetus or the litter as the experimental unit, skeletal examinations revealed statistically significant (p# 0.05) increases in incomplete ossification of several bones in both the 75 and 150 mg/kg/day dose groups compared to controls. At 25 mg/kg/day there were significant (p# 0.05) increases, compared to controls, of fetuses with incompletely ossification of these three bones only: interparietals (18.1% *vs* 35%); incompletely ossified parietals (3.4% *vs* 10.6%); and, unossified hyoids (4.7% *vs* 15.3%). The increases were also significant (p# 0.05) at 25 mg/kg/day for these three findings when the litter was used as the experimental unit.

The developmental LOAEL is 25 mg/kg/day, based on increases in incidences of incompletely ossified parietals, interparietals and unossified hyoids. The developmental NOAEL is 2.5 mg/kg/day. The developmental toxicity study in the rat is classified **Acceptable-Guideline** and does satisfy the guideline requirement for a developmental toxicity study (OPPTS 870.3700; §83-3a) in the rat.

Dose and Endpoint for Establishing RfD: 2.5 mg/kg/day based on incomplete ossification of parietals and interparietals and unossification of hyoid bones at the LOAEL (25 mg/kg/day). These effects are presumed to occur after a single dose.

Uncertainty Factor (UF): 100. Ten for intraspecies and 10 for interspecies variations

Comments about Study/Endpoint/Uncertainty Factor: The developmental effects are presumed to occur after a single exposure, and were, thus, considered to be appropriate for the acute risk assessment. This dose/endpoint is applicable only to Females 13 to 50 female subpopulation.

$$\textbf{Acute RfD} = \frac{2.5 \text{ mg/kg}}{100} = \textbf{0.025 mg/kg}$$

Dose/endpoint for General population including infants and children

An appropriate end point for this population attributable to a single exposure was not available from the oral toxicity studies.

2.2 Chronic Reference Dose (RfD)

Study selected: Subchronic oral toxicity study in the rat Guideline #: 82-1

MRID No.: 43013207

Executive Summary:

Groups of 15 male and 15 female CD Sprague-Dawley rats were fed diets containing diaminochlorotriazine (G-28273) (purity 98.2%) at concentrations of 0, 10, 100, 250, or 500 ppm for 13 weeks. The average consumption of test material was 0.7, 6.7, 16.7, or 34.1 mg/kg/day (males) and 0.7, 7.6, 19.7, or 40.2 mg/kg/day (females). All animals survived to study termination. No treatment-related clinical signs of toxicity including ocular lesions were seen at any dose level. At 500 ppm, mean body weights of male rats were lower than controls during most of the study period, decreasing to 87% of controls at week 12. Body weight gain at week 12 was 82% of controls for males receiving 500 ppm, and 85% and 83% of controls for females receiving 250 and 500 ppm, respectively. No treatment-related effects on body weight or body weight gain were seen at the lower doses in either sex. Food consumption was not affected by administration of the test material. There were no biologically significant effects on hematology, clinical chemistry, urinalysis, and gross or histopathology at any dose level. Although several organ weight changes were observed, there were no histologic or functional correlates. Estrous cycle data indicated a treatment-related effect at doses of $100 ppm. The effects, generally more pronounced on days 70-85 than on days 14-28 and 42-56, included lengthening of the estrus cycle and/or an increased incidence of rats exhibiting cycles with persistent estrus and/or diestrous. There were no apparent effects on serum levels of estradiol, progesterone, prolactin, and corticosterone. **Based on estrous cycle effects in female rats, this study provided a NOAEL = 10 ppm (0.7 mg/kg/day) and a LOAEL = 100 ppm (7.6 mg/kg/day).**

Classification: This study is classified as Core-Guideline and satisfies the guideline requirement for a subchronic dietary toxicity study (82-1) in rats.

Dose and Endpoint for Establishing RfD: 0.7 mg/kg/day based on estrus cycle alterations in the next highest dose.

Uncertainty Factor(s): 300. Ten for intraspecies, 10 for interspecies variations and 3 for use of a subchronic (90 day) study.

Comments about Study/Endpoint/Uncertainty Factor: Though only a three month study, this study measured a sensitive neuroendocrine endpoint (estrous cycle alterations), and is thus, the most appropriate study to use in selecting the chronic RfD. The chronic study in dogs is not selected as the estrous cycle alterations seen in the rat study are deemed to be more sensitive endpoints than the alterations seen in the chronic dog study.

An additional 3x uncertainty factor is proposed to account for the short duration of the study. Examination of estrous cycle data from other studies indicates that estrous cycle alterations continue to deteriorate beyond 3 months. Beyond 6 months of exposure the differences in estrous cycle deterioration between treated animals and controls no longer widens as the control animals begin the normal reproductive aging process.

Chronic RfD = $\frac{0.7 \text{ mg/kg/day}}{300}$ = **0.002mg/kg/day**

2.3 Occupational/Residential Exposure

2.3.1 Short-Term (1-7 days) Incidental Oral Exposure

Study Selected: Developmental Toxicity (Rat) Guideline #: 83-3

MRID No.: 41392402

Executive Summary: See above under, "Acute Reference Dose (RfD)".

Dose and Endpoint for Risk Assessment : 25 mg/kg/day, based on decreased body weight gain during dosing seen at the next highest dose.

Comments about Study/Endpoint: This is the same study upon which the Acute RfD was based, but the maternal NOAEL is used (rather than the developmental NOEL) since the endpoint is appropriate for the population (infants and children) of concern.

Intermediate-Term (7 Days to Several Months) Incidental Oral Exposure

Study Selected: 13/52 week dog Guideline #: 83-1

MRID No.: 41392401

Executive Summary:

Diaminochlorotriazine was fed to male and female dogs at dietary levels of 0,5,100, or 1500 ppm for 13 or 52 weeks. Because of severe toxicity at the highest dose, which was evident after 6 weeks of treatment, the high-dose dogs were fed a diet containing 750 ppm. Females tolerated this dose level and received 750 ppm until termination at 13 or 52 weeks, or through 13 weeks followed by a 39-

week recovery period. Since males continued to exhibit signs of toxicity at 750 ppm, they were fed untreated diet for 9 weeks through 13. Four male dogs were then placed again on a diet containing 750 ppm until termination at 52 weeks.

The mean daily doses for male dogs receiving dietary levels of 5, 100, and 1500/750 ppm for 52 weeks were 0.187, 3.61, and 24.1 mg/kg/day, While the doses were 0.195, 3.43, and 32.7 mg/kg/day for females receiving the same dietary levels.

Among the high-dose dogs, five males and two females were sacrificed moribund during the treatment period. Moribundity was attributed to impairment of heart function, the primary treatment-related effect of diaminochlorotriazine, which was accompanied by several clinical and pathological changes. Pathological cardiac findings included enlargement, softness, thickened valves, lesions, distension, red/dark color, thrombosis, chronic myocarditis, necrosis, inflammation, hemorrhage, and hemosiderosis. Secondary treatment-related changes in the high-dose animals were seen in the liver (enlargement, congestion, centrilobular fibrosis/atrophy, bile stasis, necrosis, hemosiderosis, red/dark color, lesions, adhesions, mottling, and rough texture); testes (hypospermatogenesis and hypospermia); thymus (atrophy); bone marrow (hyperplasia); and pericardium, thoracic, and abdominal cavities (fluid accumulation). Recovery females did not exhibit any clinical ophthalmological signs of cardiac impairment. Other effects at the high dose included decreased body weight gains in males and females dosed for 6 weeks; increased mean spleen, liver, and kidney weights; anemia with accompanying reticulocytosis (a reversible effect); decreases in albumin, calcium and total cholesterol levels; nonsignificant increase in lactic acid dehydrogenase activity ; and elevations of platelet levels. High-dose males continued to lose weight when the dose was lowered to 750 ppm. Severe anemia with reticulocytosis was noted in only one of the two recovery females. The effects of diaminochlorotriazine on cholesterol levels and erythroid parameters were reversible as were noted in almost all animals of both sexes and beginning at week 6 and extending until week 14.

No adverse effects were observed at dietary levels of 5 or 100 ppm. Administration of dietary levels of $ 750 ppm to dogs is associated with symptomatology of cardiac impairment.

For both male and female dogs, the NOAEL is 100 ppm (3.61 mg/kg/day for males and 3.43 mg/kg/day for females) and the LOAEL is 750 ppm (24.1 mg/kg/day for males and 32.7 mg/kg/day for females), based on tremors, heart alterations and mortality.

This study is classified as **Acceptable-Guideline** and <u>does</u> satisfy the 83-1 guideline requirement for a chronic toxicity study in the dog.

<u>Dose and Endpoint for Risk Assessment:</u> 3.4 mg/kg/day based on tremors, heart alterations and morbidity seen at the next highest dose.

<u>Comments about Study/Endpoint:</u> Although the subchronic rat study has a lower NOAEL, the dog study is selected because the endpoint in the subchronic rat study (estrus cycle alterations) is not relevant to the population of concern (infants and children).

2.3.2 <u>Dermal Absorption</u>

Based on SAR, the studies and dermal absorption factor selected are identical to those

selected for atrazine

Dermal Absorption Factor: **The committee recommended a dermal absorption factor of 6% (rounded up from 5.6%).** This factor is based on a human study (MRID 44152114) in which 10 human volunteers were exposed to a single topical dose of [triazine ring-U-^{14}C]atrazine (94.3-96.3% a.i., 98.0-98.4% radiochemical purity) at 6.7 (4 volunteers) or 79 : g/cm^2 (6 volunteers) for 24 hours; equivalent to 0.1667 and 1.9751 mg of [14C] atrazine for the low and high doses, respectively. After 24 hours the atrazine was removed and determination of percent absorbed occurred was determined 168 hours (7 days) after the commencement of exposure. The maximum percent absorbed in this study was 5.6% of the dose in the lower dose group. Because the maximum percent absorbed is being used and because an ample amount of time (168 hours) was allowed for absorption to occur, 6% is deemed to be a protective estimate of dermal exposure.

2.3.3 Short-Term Dermal (1-7 days) Exposure

Study Selected: Developmental Toxicity in Rats § 83-3

MRID No.: 41392402

Executive Summary: See above under "Acute Reference Dose RfD"

Dose and Endpoint for Risk Assessment: 2.5 mg/kg/day based on incomplete ossification of parietals and interparietals and unossification of hyoid bones.

Comments about Study/Endpoint: No dermal toxicity studies are available. The dosing regimen in this study is appropriate for the exposure period of concern. Since an oral NOAEL was selected, the 6% dermal absorption factor should be used for route-to- route extrapolations.

2.3.4 Intermediate-Term Dermal (7 Days to Several Months) Exposure

Study Selected: Subchronic oral toxicity study in the rat §82-1

MRID No.:43013207

Executive Summary: See above under "Chronic Reference Dose (RfD)"

Dose/Endpoint for Risk Assessment: 0.7 mg/kg based on estrus cycle alterations in the next highest dose.

Comments about Study/Endpoint: The treatment regimen in this study is appropriate for the

exposure period of concern. Since an oral NOAEL was selected, the 6% dermal absorption factor should be used for route-to- route extrapolations.

2.3.5 Long-Term Dermal (Several Months to Life-Time) Exposure

Study Selected: Subchronic oral toxicity study in the rat §82-1

MRID No.:43013207

Executive Summary: See above under "Chronic Reference Dose (RfD)"

Dose/Endpoint for Risk Assessment: 0.7 mg/kg based on estrus cycle alterations in the next highest dose.

Comments about Study/Endpoint: No dermal toxicity studies are available. This is the same study/endpoint as was proposed under "Chronic Reference Dose (RfD)". Since an oral NOAEL was selected, the 6% dermal absorption factor should be used for route-to- route extrapolations.
An additional 3x uncertainty factor is proposed to account for the short duration of the study.

2.3.6 Inhalation Exposure (All Durations)

No inhalation studies are available for evaluation. Therefore the HIARC selected the oral NOAELs for inhalation risk assessments. Since an oral dose is used, risk assessment should follow the route-to-route extrapolation as below:

Step I. The inhalation exposure component (i.e ：g a.i./day) using 100% absorption rate (default value) and application rate should be converted to an equivalent oral dose (mg/kg/day).

Step II. The dermal exposure component (mg/kg/day) using a 6% dermal absorption rate and application rate should be converted to an equivalent oral dose. This dose should then be combined with the oral equivalent dose in Step I.

Step III. The combined oral equivalent dose from Step II should then be compared to the oral NOAELs to calculate MOEs. The NOAELs are as follows:

For short term: 2.5 mg/kg/day
For intermediate term: 0.7 mg/kg/day
For chronic exposures: 0.7 mg/kg/day

2.3.7 Margins of Exposure for Occupational/Residential Risk Assessments

For short and intermediate term occupational exposure risk assesment the level of concern is an MOE of 100. For long term exposure risk assesssments, the level of concern is an MOE of 300. This includes the conventional 100 for intera and intraspecies variation and an additional three for the use of a subchronic study.
The level of concern (MOEs) for residential exposure will be determined by the FQPA SF committee.

3 CLASSIFICATION OF CARCINOGENIC POTENTIAL

3.1 Combined Chronic Toxicity/Carcinogenicity Study in Rats: This study not available.

3.2 Carcinogenicity Study in Mice: This study not available.

3.3 Classification of Carcinogenic Potential: DACT has not been classified as to its carcinogenic potential by the HED Cancer Peer Review committee. The HED Metabolism Committee concluded in a September 29, 1995 meeting that: "For Atrazine, the residues of concern for cancer dietary risk are parent and chloro metabolites".

4 MUTAGENICITY

DACT was negative in the *Salmonella*/Ames assay when evaluated up to the limit concentration of 5000 ：g per plate in tester strains TA 98, TA100, TA1535, and TA1537 with and without metabolic activation from the S9 fraction of Aroclor-treated rats (MRID 40722302). This study is classified as **Acceptable-Guideline**.

In an UDS assay using isolated human fibroblasts, DACT was negative up to 600 ：g/mL (which exceeded the solubility limit of 400 ：g/mL) (MRID 40722303). This study is classified as **Acceptable-Guideline**.

5 FQPA CONSIDERATIONS

5.1 Adequacy of the Data Base Though the entire toxicology database consists of five studies,

the toxicology database for DACT was considered adequate by the HIARC for consideration of factors under FQPA. Because of the structural similarities between atrazine and DACT, it is assumed that DACT will not display any qualitative differences in factors of concern in regards to FQPA. Thus, information from the atrazine toxicology database may be used to gain a better understanding of potential DACT toxicities.

5.2 **Neurotoxicity** Indications of possible neurotoxicity were not evident in the submitted guideline studies. Decreased brain weights seen in the high dose of the 90 day rat study (MRID 43013207) were deemed by HIARC to be secondary to overall body weight decreases. Tremors seen in the high dose of the 52 week dog study (MRID 41392401) were deemed by HIARC to be a secondary to the overall high level of general toxicity seen in the high dose dogs. Special studies submitted by the registrant (MRIDs 44152102 and 43934406) and published in the open literature (Cooper, *et al.* 2000. Atrazine disrupts the hypothalamic control of pituitary- ovarian function. Tox. Sci. 53: 297-307 [MRID 45166902]) provide evidence of atrazine-associated neurotoxicity. The neurotoxicity seen in these studies was a central nervous system (CNS) toxicity (specifically, neuroendocrine alterations at the hypothalamus). It can be assumed that atrazine will have similar effects and a submitted study (MRID 45058701) showed that DACT exposure to female Sprague-Dawley rats for 28 days did attenuate the proestrous LH surge (attenuation of the LH surge is indicative of the types of CNS defects described in the previous few sentences).

5.3 **Developmental Toxicity** A developmental toxicity study in the rat is available (MRID 41392402). The executive summary for this study is shown above under "Acute Reference Dose (RfD)"

5.4 **Reproductive Toxicity** A two-generation reproduction study is not available.

5.5 **Additional Information from Literature Sources** An open literature publication (Cooper, R.L., Robinette CL, and Stoker T.E., 1999. Maternal exposure to atrazine during lactation suppresses suckling-induced prolactin release and results in prostatitis in the adult offspring. *Tox. Sci*. 1999 Nov; 52(1):68-79 [MRID 45166902,]) has demonstrated that exposure of a lactating dam to atrazine during the days shortly after parturition may result in increased incidence and severity of prostate inflammation in male offspring. Other work from the Agency's NHEERL laboratory has indicated that atrazine exposure to immature rats may delay the onset of puberty (Stoker, *et al.*, 2000. The Effects of Atrazine on Puberty and Thyroid Function in the Male Wistar Rat: An Evaluation in the Male Pubertal Protocol. Submitted. Laws, *et al.* 2000. The effects of atrazine on puberty in female Wistar rats: An evaluation in the protocol for the assessment of pubertal development and thyroid function. Submitted). The mode of action for these two effects (prostate inflammation and delayed puberty) is believed to be similar to the mode of action described for atrazine-associated cancer and involves the CNS neuroendocrine alterations described in the HED CPRC document

(specifically, neuroendocrine alterations at the hypothalamus).
Although the above described studies use atrazine rather than DACT, it is assumed that DACT would have similar effects.

5.6 **Determination of Susceptibility** HIARC concluded that an increased quantitative susceptibility was seen in the developmental study (evidence of increased quantitative susceptibility was seen in the developmental toxicity study in the rat. In this study the LOAEL/NOAEL for maternal effects was 75/25 and the LOAEL/NOAEL for developmental effects was 25/2.5). The literature studies discussed above under section 5.5 provide evidence of increased susceptibility.

5.7 **Recommendation for a Developmental Neurotoxicity Study**

5.7.1 Evidence that suggest requiring a Developmental Neurotoxicity study:

Special studies and an open literature study mentioned above indicate a neuroendocrine toxicity in the CNS of rats following atrazine exposure. Such alterations would also be expected to be seen following DACT exposure.

5.7.2 Evidence that **do not** support a need for a Developmental Neurotoxicity study:

Overt signs of neurotoxicity seen in the submitted guideline studies using DACT (decreased brain weight in a 90-day rat study; tremors in a chronic dog study) were deemed by HIARC to be secondary to general or systemic toxicity.
The avaible studies have not indicated any disruption of thyroid function following DACT exposure.
Evidence of neurotoxicity was seen following atrazine exposure. It would be expected that DACT would also display similar neurotoxicity. Evidence of neurotoxicity following exposure to a compound is frequently seen as evidence that supports the need for a Developmental Neurotoxicity study (DNT). However, numerous studies have been conducted which have described and defined this atrazine-associated neurotoxicity. The neurotoxicity seen following atrazine exposure is CNS neuroendocrine toxicity. This CNS neuroendocrine toxicity has been well-defined through a series of registrant submitted studies and studies performed by EPA scientists at NHEERL. Many of the parameters measured in the DNT are behavioral in nature, or are effects on the peripheral nervous system (PNS). Tests conducted in a DNT are those such as motor activity tests, auditory startle tests, and learning and memory tests. The neurotoxicity associated with atrazine exposure has been well-defined, and does not involve behavioral alterations or the PNS.
Certain measures performed in the DNT (such as determination of onset of developmental landmarks and neuropathology) would be useful in examining this CNS neuroendocrine toxicity. However, special studies designed specifically to examine these endpoints would be much more useful in this regard as protocols could be designed around the desired endpoints.

Therefore, HIARC determined that a DNT is not required. Instead, the HIARC reccommended that studies examining the specific CNS alterations described in the studies conducted by the registrant and the Agency's NHEERL labs, be performed.

6 HAZARD CHARACTERIZATION

DACT is the terminal metabolite of atrazine, simazine and propazine. Both plants and mammals are capable of metabolizing these compounds to DACT, though in mammals DACT is a major metabolite while in plants it is only a minor metabolite. Bacteria are also able to metabolize atrazine, simazine, and propazine to DACT.

Guideline subchronic, chronic, and developmental studies did not indicate any particular target organ for toxicity. Several studies have indicated that atrazine is associated with mammary and pituitary tumors in females of the Sprague-Dawley strain of rat. The HED metabolism committee has stated that the chlorometabolites of atrazine (including DACT) are also of carcinogenic concern. Special studies designed to elucidate a mode of action of for this carcinogenic effect of atrazine have demonstrated that the hypothalamus appears to be a target organ. Neuroendocrine alterations of the hypothalamic-pituitary axis of rodents following atrazine exposure have been well-described both in studies submitted by the registrant and in studies conducted by EPA labs. These alterations are seen in chronic studies at low doses and in shorter term studies at higher doses. Because of the structural similarities of DACT to atrazine, it is assumed that DACT exposure will also be associated with these neuroendocrine alterations. A recently submitted study (MRID 45058701) has confirmed that at least some of the neuroendocrine effects seen following atrazine exposure are seen following DACT exposure. In this study DACT was found to attenuate the proestrous afternoon LH surge in Sprague-Dawley female rats after 28 days exposure. Atrazine also attenuates the LH surge in this strain of rat and does so at does similar to the doses at which DACT attenuates the surge.

Evidence of an increased susceptibility to infants and children from DACT exposure was seen in the rat developmental toxicity study. The LOAEL/NOAEL for maternal effects was 75/25 and the LOAEL/NOAEL for developmental effects was 25/2.5 in this study.

The mutagenicity database for DACT is adequate and indicates that DACT is not mutagenic.

7 DATA GAPS

DACT is metabolite of registered pesticides and is not a registered pesticide itself. Registration is not being sought for DACT. Thus, a full toxicology database consisting of guideline FIFRA Series 81 - 85 or OPPTS 870 Series studies are not required for DACT. Some guideline studies using DACT have been submitted to the agency. These studies, in conjunction with the

toxicology studies from atrazine - the structurally similar parent of DACT - have been used by HIARC to evaluate the potential toxicity of DACT exposure.

HIARC has concluded that evidence of increased quantitative susceptibility was seen in the developmental toxicity study in the rat. In this study the LOAEL/NOAEL for maternal effects was 75/25 and the LOAEL/NOAEL for developmental effects was 25/2.5.

HIARC requires that a two-generation study employing the OPPTS Series 870 guidelines be conducted in order to more fully evaluate this increased susceptibility. Additionally, a two-generation reproductive toxicity study conducted using the 870.3800 guidelines would employ sperm measures in the male, which would be useful measures to have given the evidence of hypospermatogenesis and hypospermia seen in the chronic dog study. No evidence of increased susceptibility was seen in two rat and one rabbit developmental toxicity study using atrazine or in one two-generation study using atrazine. Because of the structural similarity between atrazine and DACT, the lack of susceptibility with atrazine is taken into consideration and a rabbit developmental toxicity study using DACT is not required at this time.

HIARC suggests that the F2 generation from the required new two-generation study be maintained for 120 days in order to evaluate incidence of prostate inflammation. Should this suggestion be followed it is recommended that Cooper, *et al.*, 1999. *Tox. Sci*. 1999 Nov; 52(1):68-79 be referred to, and that the alteration of the 870.3800 protocol be approved by HED.

8 ACUTE TOXICITY

Acute toxicity studies with DACT are not available for evaluation.

9 SUMMARY OF TOXICOLOGY ENDPOINT SELECTION

The doses and toxicological endpoints selected for various exposure scenarios are summarized below.

EXPOSURE SCENARIO	DOSE (mg/kg/day)	ENDPOINT	STUDY
Acute Dietary	NOAEL= 2.5 UF = 100	Incomplete ossification of certain cranial	Developmental toxicity study in the rat
	Acute RfD = 0.025		
Chronic Dietary	NOAEL =0.7 UF = 300	Estrous cycle alterations	90-day study in the rat
		Chronic RfD = 0.002	
Incidental Oral, Short-Term	NOAEL= 25	Decreased maternal body weight gain	Developmental toxicity study in the rat
Incidental Oral, Intermediate-Term	NOAEL= 3.4	tremors, cardiac effects, mortality	Chronic toxicity study in the dog
Dermal, Short-Term [a]	NOAEL= 2.5	Incomplete ossification of certain cranial	Developmental toxicity study in the rat
Dermal, Intermediate-Term[a]	NOAEL= 0.7	Estrous cycle alterations	90-day study in the rat
Dermal, Long-Term [a]	NOAEL= 0.7	Estrous cycle alterations	90-day study in the rat
Inhalation, Short-Term[b]	NOAEL= 2.5	Incomplete ossification of certain cranial	Developmental toxicity study in the rat
Inhalation, Intermediate-Term[b]	NOAEL= 0.7	Estrous cycle alterations	90-day study in the rat
Inhalation, Long-Term[b]	NOAEL= 0.7	Estrous cycle alterations	90-day study in the rat

a Dermal absorption rate = 6%

b Convert from oral dose using an inhalation absorption rate= 100% default